UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/674,092	08/26/2002	Marcus Keep	30-200P	1549

2292 7590 04/05/2007
BIRCH STEWART KOLASCH & BIRCH
PO BOX 747
FALLS CHURCH, VA 22040-0747

EXAMINER	
MOHAMED, ABDEL A	
ART UNIT	PAPER NUMBER
1654	

SHORTENED STATUTORY PERIOD OF RESPONSE	NOTIFICATION DATE	DELIVERY MODE
3 MONTHS	04/05/2007	ELECTRONIC

Please find below and/or attached an Office communication concerning this application or proceeding.

If NO period for reply is specified above, the maximum statutory period will apply and will expire 6 MONTHS from the mailing date of this communication.

Notice of this Office communication was sent electronically on the above-indicated "Notification Date" and has a shortened statutory period for reply of 3 MONTHS from 04/05/2007.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

mailroom@bskb.com

Office Action Summary	Application No.	Applicant(s)	
	09/674,092	KEEP ET AL.	
	Examiner	Art Unit	
	Abdel A. Mohamed	1654	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *13 October 2006*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-14 and 21-23* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-14 and 21-23* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

CONTINUED EXAMINATION UNDER 37 CFR 1.114 AFTER FINAL REJECTION

1. A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 10/13/06 has been entered.

ACKNOWLEDGMENT OF AMENDMENT, REMARKS AND STATUS OF THE CLAIMS

2. The amendment and remarks filed 09/13/06 are acknowledged, entered and considered. In view of Applicant's request claims 1, 3-6, 8 and 11-14 have been amended, claims 15-20 have been canceled and claims 21-23 have been added. Claims 1-14 and 21-23 are now pending in the application. The rejection under 35 U.S.C. 103(a) over the prior art is maintained for the reasons of record.

CLAIMS REJECTION-35 U.S.C. 112, 1st PARAGRAPH

3. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1, 2, 5, 6, 8, 9, 11-14, 22 and 23 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

Independent claim 1 and claims depending thereof as original filed contain new matter because the original specification does not appear to support for "wherein the concentration of cyclosporin is from **0.1% to 25%** by weight of the total composition, and wherein DMSO is present at least **75%** by weight in the composition" (claims 1 and 21). Also, claim 22 has no support in the originally filed specification for "wherein said composition is formulated in a unit dosage of at least **0.001 mg/kg body weight/day** to at least **1000 mg/day**". The instant specification on page 7, Example 1 discloses formulation of cyclosporin as injectable solution in which the cyclosporin has a concentration of 200 mg/ml and the DMSO has 800 mg/ml (i.e., the concentrations would have been 20% cyclosporin and 80% DMSO and not 25% cyclosporin and 75% DMSO as claimed). Similarly, the dosage ranges of the pharmaceutical formulations disclosed on page 6 are 0.001 to 50 mg/kg body weight per day, and 0.001 to 150 mg/kg body weight per day. Thus, independent claim 1 and claims depending thereof including claims 21 and 22 have no support for the limitations for "wherein the concentration of cyclosporin is from **0.1% to 25%** by weight of the total composition, and wherein DMSO is present at least **75%** by weight in the composition" (claims 1 and 21) and "wherein said composition is formulated in a unit dosage of at least **0.001**

mg/kg body weight/day to at least **1000 mg/day**" (claim 22) from the original disclosure because there is no disclosure in the specification for the concentrations and dosages ranges as now claimed. Thus, Applicant respectfully requested to either cancel all unsupported subject matter or to show where such subject matter has support from the original disclosure.

CLAIMS REJECTION-35 U.S.C. § 103(a)

3. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(f) or (g) prior art under 35 U.S.C. 103(a).

ARGUMENTS ARE NOT PERSUASIVE

4. Claims 1-14 including newly submitted claims 21-23 remain rejected under 35 U.S.C. 103(a) as being unpatentable over Kaswan (U.S. Patent No. 4,649,047) taken with Elzinga et al (Transplantation, Vol. 47, No. 2, pp. 394-395, February 1989), Broadwell et al (Science, Vol. 217, No. 4555, pp. 164-166, July 9, 1982) and Elias (U.S. Patent No. 5,807,820).

Applicant's arguments filed 09/13/06 have been fully considered but they are not persuasive. Applicant has argued that the cited reference either singularly or in combinations teach or suggest a) using DMSO in an amount of 75% by weight or greater of a pharmaceutical composition comprising cyclosporin, b) administering a pharmaceutical composition comprising DMSO and cyclosporin by injection into cerebrospinal fluid or cerebrospinal spaces of a patient as claimed in claim 3, or intravestibularly, as recited in claim 4, c) administering the pharmaceutical composition according to claim 1 by injection intravenously, intra-arterially or intraparenchymally, as recited in claim 5, or inhalationally or nasally, as recited in claim 6, d) disclosing an article of manufacture as recited in claim 8, e) disclosing a method of treating any and all of the diseases recited in claim 11, and f) disclosing a method fro inducing systemic immunosuppression in patients of transplantation or autoimmune dieses are noted and unpersuasive. Applicant has amended independent claim 1 and added new claim 21 to recite, "wherein the concentration of cyclosporin is from **0.1% to 25%** by weight of the total composition, and wherein DMSO is present at least **75%** by weight in the composition". Also, Applicant has added new claim 22 to recite, "wherein said

composition is formulated in a unit dosage of at least **0.001 mg/kg body weight/day** to at least **1000 mg/day**". However, Applicant has not shown support for the concentrations and dosage ranges as amended in claim 1 and presented as new claims 21 and 22 as discussed *supra* in the rejection under 35 U.S.C. 112, first paragraph for new matter. Thus, until Applicant provides support in the instant specification for the concentrations and dosage ranges as currently amended in claim 1 and claimed in claims 21 and 22, Applicant's arguments with respect to the concentrations and dosage ranges are unpersuasive.

In regard to the other arguments raised by Applicant, contrary to Applicant's arguments, the Examiner acknowledged in the previous Office action that the primary reference of Kaswan differs from claims 1-14 and newly submitted claims 21-23 in failing to teach a) methods for administering said cyclosporin and DMSO solution by injection into the cerebrospinal fluid, intra-ocular, intravestibular, into or adjacent to the brain or spinal cord, or intravenous, intra-arterial, intraparenchymal spaces, or orally, rectally, vaginally, urethrally, bladder cisternally, nasally, intra and peri-ocullary or dermally to a patient, b) use of an article of manufacture comprising packaging material and pharmaceutical agent wherein said pharmaceutical agent comprises DMSO and cyclosporin formulation thereof, c) a method for treating Alzheimer's disease, Parkinson's disease, sclerosis, HIV neuropathy, Guillain-Barre syndrome, neuronal transplantation, neural xenotransplantation, stroke, brain hemorrhage, brain and spine trauma, ionizing radiation, neurotoxicity of vestibulocochlear structures and retinal detachment, and d) a method for inducing systemic immunosuppression in patients with

transplantation and autoimmune disease. However, the secondary reference of Elzinga et al compares the effect of DMSO with that of the conventional olive oil vehicle on the absorption of cyclosporin following oral administration in rats. The reference states that following oral administration of CsA solution, the absorption of CsA is highly variable and incomplete, ranging from 4% to 26% of the administered dosage in one study in renal transplant recipients. Nevertheless, DMSO is an excellent organic solvent that readily penetrates most tissue membranes, acting as a "carrier" for many solutes, including various drugs. Thus, the reference clearly shows that DMSO penetrates most biological membranes with ease, and has been used as an effective carrier of drugs and other solutes and considered to be safe. The reference of Elzinga concludes by stating that the increased bioavailability of CsA following administration in DMSO is due to enhanced gastrointestinal absorption, although other effects of DMSO on CsA pharmacokinetics cannot be excluded. Complete pharmacokinetic and immunosuppression studies in humans are warranted as the use of DMSO as the vehicle for CsA could result in considerable cost savings, provided immunosuppression is not compromised (See e.g., pages 394 and 395).

Further, the secondary reference of Broadwell et al describes the morphologic effect of DMSO on blood-brain barrier. Although, the use of DMSO in the treatment of cerebral infarction, brain swelling, and spinal cord injury is controversial, however, morphological changes were observed on gross or microscopic in brain parenchyma from mice exposed to DMSO concentration of up to 15%. Brains and pituitaries from animals given 0.5 ml of DMSO intraperitoneally and 0.25 ml of DMSO intravenously at

concentrations up to 15% did not exhibit hemorrhage. Regardless of the volume, concentration and route of delivery of DMSO, the corneas, lungs, heart, kidneys, liver, and intestines of all DMSO injected mice appeared normal on gross examination at autopsy. The reference of Broadwell et al concludes by stating that the search of a safe and reliable approach for promoting the entry to the brain of blood-borne chemotherapeutic agents and antibiotics may depend on an increased understanding of the mechanism of blood-brain barrier function. Whether or not DMSO can safely and effectively open the blood-brain barrier *in vivo* to chemotherapeutic drugs and antibiotics requires further investigation. Thus, in view of the above, the reference clearly motivates one of ordinary skill in the art at the time the invention was made to use DMSO as a carrier in any drug of choice because as stated above regardless of the volume, concentration and route of delivery of DMSO, the corneas, lungs, heart, kidneys, liver, and intestines of all DMSO injected mice appeared normal on gross examination at autopsy (See e.g., pages 164 and 165). Furthermore, the reference of Elias discloses pharmaceutical compositions comprising cyclosporin wherein the cyclosporin is CsA having a concentration from 0.1 to 50% of a cyclosporin based on total weight and useful for topical application (See e.g., col. 9, line 36-37 and claims 1 and 2). Thus, the secondary references clearly show the use of DMSO as a carrier/penetrating agent in a medicinal formulation wherein the medicinal agent or formulation could be the combination of DMSO and any agent of interest, which may include cyclosporins, particularly CsA at claimed concentrations.

Therefore, in view of the above and in view of the combined teachings of the prior art, it would have been routine and conventional to one of ordinary skill in the art to which this invention pertains to administer a pharmaceutical formulation of interest to a patient in need thereof. Because the appropriate dosages and modes of administration can and will be determined by the prescribing physician and will be a result of the severity of the condition being treated as well as the response with the derivatives being administered and the age, weight, sex and medical history of the patient.

In regard to claims 8 and 9, an article of manufacture comprising packaging material and pharmaceutical agent or formulation claimed for the intended purposes for reducing or treating neuronal damage and for causing immunosuppression when administered; but, where the above reference differs from claims 8 and 9 in not teaching *per se* the formulation claimed in a packaging material and use thereof. However, it would have been obvious to package the composition required for the method into packaging material and/or kit format of the well-known commercial expediency of dong so. Therefore, in view of the above, in view of the combined teachings of the prior art, and in the absence of unexpected results or factual evidence to the contrary, modifications such as the selection of an appropriate cyclosporin and formulations of packaging material and/or kit thereof, would have resulted in the claimed invention which was *prima facie* obvious to make and use at the time it was made.

Therefore, it would have been obvious to one of ordinary skill in the art at the time the invention was made to have combined the teachings of the primary reference of Kaswan or the reference of Elzinga et al with the reference of Broadwell et al or Elias

in order to administer cyclosporin and DMSO by any one of the modes of administration recited in claims 3-6, 10, 13, 14, 21 and 22. The artisan of ordinary skill in the art utilizing the methods of Broadwell et al would have obtained the improvement when such combinations and formulations (as disclosed in the primary reference) are administered to patients suffering from the diseases or conditions recited in claims 11 and 12. Further, such features (i.e., using DMSO as a carrier on blood-brain barrier) are known or suggested in the art, as seen in the secondary reference, and including such features into the composition of the primary reference of '047 patent would have been obvious to one of ordinary skill in the art to obtain the known and recognized functions and advantages thereof. Thus, it is made obvious by the combined teachings of the prior art since the instantly claimed invention which falls within the scope of the prior art teachings would have been obvious because as held in host of cases including *Ex parte Harris*, 748 O.G. 586; *In re Rosselete*, 146 USPQ 183; *In re Burgess*, 149 USPQ 355 and as exemplified by *In re Betz*, "the test of obviousness is not express suggestion of the claimed invention in any and all of the references but rather what the references taken collectively would suggest to those of ordinary skill in the art presumed to be familiar with them".

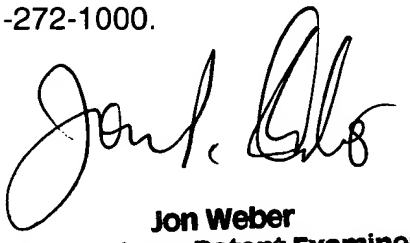
CONCLUSION AND FUTURE CORRESPONDANCE

6. No claim is allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Abdel A. Mohamed whose telephone number is (571) 272 0955. The examiner can normally be reached on First Friday off.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Tsang Cecilia can be reached on (571) 272 0562. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.



Jon Weber
Supervisory Patent Examiner

Mohamed/AAM
March 30, 2007